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10/714,333

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Anastasia Khvorova

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KALOW & SPRINGUT LLP

488 MADISON AVENUE

19TH FLOOR

NEW YORK, NY 10022

EXAMINER

EPPS FORD, JANET L

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/714,333

Applicant(s)

KHVOROVA ET AL.

Examiner

Janet L. Epps-Ford

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,38-54 and 57-87 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,38-54 and 57-87 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION**

***Response to Arguments***

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 102***

2. Claim 1, 38-54, and 57-87 remain rejected under 35 U.S.C. 102(a or e) as being anticipated by Tuschl et al. (WO 02/44321 A1).

3. Applicant's arguments filed 10/10/2007 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that although the examiner has cited an example of siRNA that meets certain of the specified criteria, the Examiner has not shown that the references teaches to apply the recited criteria. In the absence of pointing to where the reference teaches elements (c)-(e) of each of the independent claims, Applicants respectfully submit that the Examiner has not met her burden of making a *prima facie* case of novelty.

4. According to the independent claims, steps (c)-(e) comprise applying a criterion to each of said candidate siRNA sequences, (d) selecting candidate siRNA sequences from the set of candidate siRNA sequences (e) synthesizing an siRNA for the target gene. Contrary to Applicant's assertions, to the extent that the recited claims comprise steps (a)-(e), the instantly claimed methods are not limited to comprise wherein steps (a)-(e) are sequential. Tuschl et al. discloses (beginning at page 43, section 3.2.1) a method for optimizing siRNAs comprising synthesizing siRNA with variations in the 3' overhang. The method of Tuschl et al. comprises designing multiple sets of siRNA

molecules, and testing them for optimal activity. In Figure 11E, all of the antisense strands of the siRNA duplexes were synthesized to comprise the following criteria wherein: the antisense regions of these siRNA duplexes comprises a structure wherein the total number of A or U residues in the first five, the first four, and the first two nucleotides at the 5' end of the antisense region is higher than that set forth in the last five, the last four, and the last two nucleotides at the 3' end of the molecule. Moreover, the first 5' position of the antisense region has either an A or U nucleotide and the last 3' position of the antisense region has neither an A nor U nucleotide. Additionally, the antisense region includes the presence of U at position 6, the absence of A at position 15, the absence of G at position 1, and the absence of C at position 7 of the antisense sequence. This sequence comprises a GC content between about 30% and 52%, and has at least 2 A or U bases at position 1-5 of the antisense sequence. Moreover, the siRNA duplexes were synthesized to comprise different 3' overhang lengths. It was concluded that duplexes with 2-nucleotide 3' overhangs were most efficient mediating RNA interference, *however the efficiency of silencing was also sequence dependent.*

5. Therefore, contrary to Applicant's assertions, the method steps of (a)-(e) as set forth in the independent claims were met by the teachings of Tuschl et al., wherein a set of candidate siRNA molecules are designed to target a gene, the siRNA molecules are designed comprising a greater number of A or U residues in the first 1-5 nucleotides of 5' end of the antisense region than in the last 1-5 nucleotides of the 3' end, comprising between 30-52% G/C content and including the presence of U at position 6, the absence of A at position 15, the absence of G at position 1, and the absence of C at

position 7 of the antisense sequence. Furthermore, the teachings of Tuschl et al. teaches that among the siRNA duplexes designed to target luciferase, see Figure 11E, those siRNA duplexes comprising 2-nucleotide 3' overhangs were the most efficient at mediating RNA interference.

6. Applicants argued that in this example Tuschl introduced the variable of overhang size and concluded that the ability of 21-nt siRNA duplexes to mediate RNAi is dependent on the number of overhanging nucleotides or base pairs formed (see last paragraph on page 18 of the reply filed 10/10/2007). However, contrary to Applicant's assertions, the instant claims comprise steps (a)-(e), therefore the addition of a step wherein the number of 3' nucleotide overhangs is varied does not necessarily teach away from the claimed invention. Moreover, although Tuschl et al. concluded that siRNA duplexes comprising 2-nucleotide 3' overhangs were the most efficient, this example also concluded that *the efficiency of silencing was also sequence dependent* (see page 44 of Tuschl et al., last paragraph). Thus, contrary to Applicant's assertions, the teachings of Tuschl et al. clearly suggest that the sequence of the siRNA duplex plays an important role in efficiency of RNA interference, see the differences in silencing efficiency observed with other siRNA duplexes targeting luciferase mRNA, and comprising 2-nucleotide 3' overhangs in Figures 11D-H.

**Response to Amendment**

**Claim Rejections - 35 USC § 112**

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 38-54, and 57-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

9. Applicants have amended the instant claims to recite wherein the sense region and said antisense region form a duplex region of 19-25 nucleotide base pairs or a duplex region of 19-30 nucleotide base pairs. Moreover, Applicants have amended the claims to require wherein the specific nucleotide positions recited in the claims correspond to positions ***within the "duplex region."***

10. As support for this amendment, in the reply filed 10/10/07, pages 15-16, applicants assert: "[A]pplicants have made explicit what was implicit, that when comparing the number of A and U nucleotides one does not consider overhang regions of an siRNA duplex if present." Moreover, Applicants assert the following:

Support for these amendments may for example be found in paragraphs: [0212] directing consideration of "low internal thermodynamic stability of the duplex at the 5'-antisense (AS)"; [0214] noting that when considering GC content one does not consider overhangs; and [0237] noting "the frequency of A/U bp was determined for each of the five terminal positions of the duplex"

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Contrary to Applicant's assertions, with the exception of the G/C content, there is no support for the amendment to the claims to recite wherein the criterion requiring wherein the number of A and U nucleotides present in the first five, first four, first three, or the first nucleotide positions at the 5' terminus of the antisense region is higher than that present in the last five nucleotide positions at the 3' terminus of the antisense region, occurs within "said duplex region." The references to the specification does not provide adequate support for the claims as presently amended, there is support for a duplex region of 19 base pairs, however there is no support for siRNA molecules comprising a "**duplex region**" of either 19-25 or 19-30 nucleotides in length.

Moreover, it is unclear that the term "duplex" recited in the passage describing the frequency of A/U bp (paragraph [0237]) was actually intended to be considered a "duplex region" as argued by Applicants, wherein the duplex does not encompass overhangs. It is possible that the term duplex used in paragraph [0237] was intended to refer to something other than a stabilized duplex between polynucleotide strands that are 100% complementary as defined in paragraph [0118]. For example, it is possible that the duplex referred to in paragraph [0237] was intended to encompass a region comprising mismatches as overhangs wherein the polynucleotide strands are substantially complementary, and having 79% or greater complementarity (see also paragraph [0118]).

Furthermore, in regards to the various sequence specific criteria set forth in claim 43 and 68 (and those claims dependent therefrom), there is no support in the specification as filed that requires that these sequence criteria are to be located within

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the antisense sequence within the duplex region of the candidate siRNA molecule or siRNA sequence.

Applicant's amendment to the claims is therefore considered new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

***Conclusion***

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.



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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/  
Primary Examiner  
Art Unit 1633

JLE